UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,529	05/06/2002	Christopher Elkins	5470-269	4127

20792 7590 08/02/2005

MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,529	ELKINS, CHRISTOPHER	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *4,6,7,11-13,19-22,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,8-10,14-18,23-25 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/25/05 & 5/6/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence report (1)*.

DETAILED ACTION

Preliminary Amendments

1) Acknowledgment is made of Applicant's amendments filed 01/09/02, 10/02/03 and 04/25/05. With these, Applicant has amended the specification.

Election

2) Acknowledgment is made of Applicant's election filed 04/25/05 of invention I, claims 1-5, 8-10, 14-18, 23-25 and 28, drawn to a polynucleotide and the election of the polynucleotide species of SEQ ID NO: 1 (claims 1a, 3, 5, 17, 18 and 24), in response to the written lack of unity mailed 03/23/05. Applicant's election of invention I is with traverse, but species election is without traverse. Applicant's traversal is on the grounds that: (a) claims of inventions I-V are linked by a single general inventive concept under PCT Rule 13.1; (b) claims of inventions I-V are joined by the unifying inventive concept of the DsrA polynucleotides which feature is novel over the art; (c) the sequence from Fleischmann *et al.* does not encode a DsrA; (d) a BLAST search between the *H. ducreyi* DsrA ORF (SEQ ID NO: 1) versus the complete database of *H. influenza* genes with substantial similarity to DsrA finds no *H. influenza* genes with substantial similarity to DsrA; (e) the evidence to date supports the proposition that *H. influenza* does not have a DrsA gene at all; (f) the sequence from Fleischmann *et al.* would not hybridize to SEQ ID NO: 1 under stringent conditions and does not encode a DsrA; and (g) given the low degree of sequence similarity between SEQ ID NO: 1 and the sequence of Fleischmann *et al.*, the two sequences would not hybridize to each other under 'high' stringency conditions 'as recited in claim 1'.

Applicant's arguments have been carefully considered, but are not persuasive. Contrary to Applicant's assertion, claim 1 does *not* recite the stringency conditions to be 'high'. Instead, claims 1 includes the phrase: 'polynucleotides that hybridize to DNA of (a) ... above under stringent conditions'. The limitation 'stringent conditions' is not limited to high stringent conditions, but also encompasses low and medium stringency conditions. The limitation 'DsrA' as recited in the instant claims has no structure or size limit, and therefore encompasses DsrA of any length. The second full paragraph on page 30 of the instant specification in fact indicates that the recitation 'DsrA' is not limited to the 'entire DsrA protein', but encompasses DsrA fragments and/or antigenic determinants. Clearly, Fleischmann's (*Science* 269: 496-512, 1995)

DETAILED ACTION

Preliminary Amendments

1) Acknowledgment is made of Applicant's amendments filed 01/09/02, 10/02/03 and 04/2/5/05. With these, Applicant has amended the specification.

Election

2) Acknowledgment is made of Applicant's election filed 04/25/05 of invention I, claims 1-5, 8-10, 14-18, 23-25 and 28, drawn to a polynucleotide and the election of the polynucleotide species of SEQ ID NO: 1 (claims 1a, 3, 5, 17, 18 and 24), in response to the written lack of unity mailed 03/23/05. Applicant's election of invention I is with traverse, but species election is without traverse. Applicant's traversal is on the grounds that: (a) claims of inventions I-V are linked by a single general inventive concept under PCT Rule 13.1; (b) claims of inventions I-V are joined by the unifying inventive concept of the DsrA polynucleotides which feature is novel over the art; (c) the sequence from Fleischmann *et al.* does not encode a DsrA; (d) a BLAST search between the *H. ducreyi* DsrA ORF (SEQ ID NO: 1) versus the complete database of *H. influenza* genes with substantial similarity to DsrA finds no *H. influenza* genes with substantial similarity to DsrA; (e) the evidence to date supports the proposition that *H. influenza* does not have a DrsA gene at all; (f) the sequence from Fleischmann *et al.* would not hybridize to SEQ ID NO: 1 under stringent conditions and does not encode a DsrA; and (g) given the low degree of sequence similarity between SEQ ID NO: 1 and the sequence of Fleischmann *et al.*, the two sequences would not hybridize to each other under 'high' stringency conditions 'as recited in claim 1'.

Applicant's arguments have been carefully considered, but are not persuasive. Contrary to Applicant's assertion, claim 1 does *not* recite the stringency conditions to be 'high'. Instead, claims 1 includes the phrase: 'polynucleotides that hybridize to DNA of (a) ... above under stringent conditions'. The limitation 'stringent conditions' is not limited to high stringent conditions, but also encompasses low and medium stringency conditions. The limitation 'DsrA' as recited in the instant claims has no structure or size limit, and therefore encompasses DsrA of any length. The second full paragraph on page 30 of the instant specification in fact indicates that the recitation 'DsrA' is not limited to the 'entire DsrA protein', but encompasses DsrA fragments and/or antigenic determinants. Clearly, Fleischmann's (*Science* 269: 496-512, 1995)

isolated gene comprising the nucleotide sequence, CGCACCTTTAACGGCTTAATTTTAGAACATTTAGAA encodes the DsrA, ArgThrPheAsnGlyLeuIleLeuGluHisLeuGlu. This prior art nucleotide is expected to hybridize with the instantly recited SEQ ID NO: 1 at least under low stringency conditions. See also the teachings of Skurnik *et al.* (*Mol. Microbiol.* 3: 517-529, 1989 – Applicants' IDS) cited below under art rejection(s). Therefore, as set forth in the written lack of unity mailed 03/23/05, the special technical feature of the first claimed product of invention I does not define over the prior art. For this reason, the lack of unity held in the instant application is proper and is hereby made FINAL.

Claims 24 and 28, previously not included in the lack of unity grouping, are now placed in invention I.

Status of Claims

3) Claim 28 has been amended via the amendment filed 01/09/02.

Claim 24 has been amended via the amendment filed 04/25/05.

Claims 1-28 are pending.

Claims 4, 6, 7, 11-13, 19-22, 26 and 27 are withdrawn from consideration as being directed to non-elected inventions or species. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 1-3, 5, 8-10, 14-18, 23-25 and 28 are under examination. A First Action on the Merits is issued for these claims.

Sequence Listing

4) The raw sequence listing submitted in this application has been entered on 10/09/2003.

Information Disclosure Statements

5) Acknowledgment is made of Applicant's Information Disclosure Statements filed 04/25/05 and 05/06/02. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Priority

6) The instant application is a national stage 371 application of the international application PCT/US00/18834 filed 07/07/00 and claims priority to the provisional application 60/143257 filed 07/09/1999.

Specification - Informalities

7) The specification of the instant application is objected to for the following reasons:

(A) To be consistent with the drawings for Figures 5A and 5B, Applicants should refer to 'Figure 5' in line 1 on page 5 of the instant specification as --Figures 5A and 5B--.

(B) The use of the trademark in the instant specification has been noted. For example, see line 18 of page 24: 'Immunex'; line 20 on page 24: 'Invitrogen'; line 32 on page 30: 'Marcol'; and last line on page 30: 'Adjuvax'. The recitation should be capitalized wherever it appears or be accompanied by the generic terminology. See M.P.E.P 608.01(V) and Appendix l. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks. It is suggested that Applicant examine the whole specification to make similar corrections to trademark recitations, wherever such recitations appear.

(C) On page 21, line 22, the address of the American Type Culture Collection is incorrect. Effective 23 March 1998, ATCC has a new address: 10801 University Boulevard, Manassas, VA 20110-2209. Amendment to the specification is suggested to reflect this. It is suggested that Applicant examine the whole specification to make similar correction to the address, wherever it appears.

Rejection(s) under 35 U.S.C. § 101

8) 35 U.S.C. § 101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this cycle.

9) Claims 14, 15, 9 and 10 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claims 14 and 15 and claim 9 and 10, as written, do not sufficiently distinguish over nucleic acids or oligonucleotides and cells as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty, 447 U.S.*

303, 206 USPQ 193 (1980). The claim(s) should be amended to indicate the hand of the inventor, e.g., by insertion of 'An isolated' if support for such a limitation exists in the specification. See MPEP 2105.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

10) Claims 23-25 and 28 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a composition comprising an isolated polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1 and a pharmaceutically acceptable carrier, and for a composition comprising an expression vector comprising the isolated polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1 and a pharmaceutically acceptable carrier, does not reasonably provide enablement for a 'vaccine' composition comprising the polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1, DsrA-encoding polynucleotides that hybridize thereto under 'stringent' conditions, or DsrA-encoding polynucleotides that differ from these polynucleotides due to the degeneracy of the genetic code, and for a 'vaccine' composition comprising an expression vector comprising the isolated polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1, DsrA-encoding polynucleotides that hybridize thereto under stringent conditions, or DsrA-encoding polynucleotides that differ from these polynucleotides due to the degeneracy of the genetic code, as claimed, and for a method for inducing a 'protective' immune response in a subject at risk of developing *H. ducreyi* infection comprising administering to the subject said vaccine in an amount sufficient to induce an immune response, as claimed currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and

- The breadth of the claims.

In the instant case, the nature of the invention is related to a DNA vaccine comprising a polynucleotide and a method of inducing 'protective immune response' in a subject at risk of developing *H. ducreyi* infection by administering the DNA vaccine. A vaccine 'must by definition trigger an immunoprotective response in the host vaccinated; mere antigenic response is not enough'. *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A review of the instant specification indicates the following. The last part of page 31 of the specification describes that the vaccination is not limited to 'naked DNA vaccines' or 'vector vaccines' and that when administered, the vaccine induces an active and protective immune response against unmodified cancer cells. This statement is not relevant to the claimed invention. Furthermore, there is absolutely no evidence or enabling disclosure within the instant specification showing that a vaccine composition comprising the polynucleotide of SEQ ID NO: 1 or a degenerate thereof encoding a full length DsrA, or a DsrA fragment or peptide, or an expression vector comprising such a polynucleotide, indeed induced an active and 'protective' immune response in any subject. The state of the art indicates that *H. ducreyi,* is the causative agent of the sexually transmitted genital ulcer disease, chancroid, which is known in the art to survive intracellularly in host granulocytes, and monocytes/macrophages. For instance, see title and abstract of Johansson *et al. Infect. Immun.* 70: 899-908, February 2002. The isolated polynucleotide from the base claim that is comprised within the vaccine composition claimed in claim 23 is not required to be associated with a host promoter or non-host promoter. It is unlikely that the nucleic acid molecule alone, without an appropriate promoter, would express the DsrA polypeptide or an immunogenic fragment of the polypeptide in any host. Whether or not the polynucleotide itself is a 'protective' antigen which induces polynucleotide-specific antibodies and interacts somehow with the intracellular DNA after gaining access inside the cells is not known or described. There is absolutely no evidence within the instant specification that the naked nucleic acid molecule as recited somehow got expressed *in vivo*, with or without a host promoter, in any subject to produce the DsrA polypeptide, or an immunogenic fragment thereof, which induced 'protective immune response' in a subject at risk of developing *H. ducreyi* infection. No method and working examples are disclosed in the instant application whereby the recited polynucleotide or an expression vector comprising the same, is demonstrated to be expressed *in vivo* in a mammalian host thus encoding *in vivo* the full length DsrA polypeptide or

an immunogenic fragment thereof in the host, wherein DsrA polypeptide or fragment thereof 'protected' the host by infection with a virulent *H. ducreyi* isolate. No part of the instant specification establishes that the recited polynucleotide molecule and an expression vector comprising the same were indeed made that were able to induce 'protective' immune response in a host to whom it was administered as a 'vaccine' composition. The disclosure in the specification is merely an invitation to an artisan to use the current invention as a starting point for further experimentation. The induction of a 'protective immune response' against chancroid in a host by administration of a vaccine composition comprising the isolated polynucleotide as recited in the instant claims is highly complex and unpredictable. Relevant literature reveals that the field of protective immunity in chancroid infection is still evolving. As of the year 2000, the major goal in the field of chancroid research was to identify antigens of *H. ducreyi* that are immunogenic and that could form the basis of a vaccine against *H. ducreyi* infection. For instance, see the abstract of Lewis DA (*AIDS Patient Care STDS* 14: 19-36, January 2000), which stated that 'a vaccine, **if** shown to be effective in decreasing the prevalence of chancroid, **could** have the added benefit of slowing down' the incidence of chancroid which is a co-factor for HIV transmission [Emphasis added]. A review of art in the field of DNA vaccines reflects unpredictability and inefficiency. For instance, McCormick *et al.* (US 20040033585) teach that naked nucleic acid vaccines are 'very inefficient' and result in 'unpredictable immune responses' (see paragraph 0125). McCormick *et al.* further teach that DNA subunit vaccines often fail to elicit antibodies (see paragraph 0006). Additionally, the state of the art recognizes the major challenge of delivering DNA to the target tissues and transporting it to the cell nucleus to enable the required protein to be expressed. For example, see paragraph 1 on page 1170 of Phillips AJ. *J Pharm. Pharmacology* 53: 1169-1174, 2001. Phillips further taught that although some evidence of gene transfer has been seen in patients, DNA administration has generally been inadequate for a meaningful clinical response (see abstract of Phillips A). Phillips identified the problem to be two-fold: (a) a system must be designed to deliver DNA to a specific target and to prevent degradation within the body, and (b) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (see paragraph 1 on page 1170 of Phillips, 2001). Thus, DNA vaccination is unpredictable and complex wherein one of skill in the art may not necessarily be able to introduce and express

the DsrA nucleic acid or a part thereof in the cells of a mammalian host, or be able to produce the DsrA polypeptide or an immunogenic fragment thereof in that host such that the polypeptide, or immunogenic fragment thereof induces a 'protective immune response' in a subject at risk of developing *H. ducreyi* infection. The specification does not enable a DsrA nucleic acid-containing vaccine composition that induces a 'protective immune response' in a subject at risk of developing *H. ducreyi* infection. Therefore, due to the lack of direction/guidance and lack of enabling disclosure and working examples in the instant specification, the complex nature of the invention, the lack of evidentiary support in the specification enabling the claimed nucleic acid-containing composition as a prophylactic vaccine composition, the unpredictability known in the art of transferring genes into host's cells such that therapeutic or prophylactic levels of a polypeptide or a fragment thereof are expressed *in vivo* in the host so as to 'protect' the host against *H. ducreyi* infection, the still evolving nature of the state of the art on protective immunity in chancroid, the breadth of the claims, and the large quantity of experimentation necessary, undue experimentation would have been required by one of skill in the art to make and use the invention or to reproducibly practice the invention as claimed. The production and use of a DsrA nucleic acid-containing 'vaccine' composition that is capable of inducing a 'protective immune response' in a subject against a homologous or a heterologous *H. ducreyi* strain is well outside the realm of routine experimentation. The claims are viewed as not meeting the enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

11) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

12) Claims 1-3, 5, 8-10, 14-18, 23-25 and 28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claims 1-3, 5, 10, 17 and 18 are vague and indefinite in the use of the abbreviation 'DsrA' in the claim language, because it is unclear what does 'DsrA' stand for. It is suggested that Applicant recite the full terminology at first occurrence of the limitation in the base claim with the abbreviated term retained within the parentheses.

(b) Claim 1 is vague and indefinite in the limitation 'stringent conditions', because it is unclear what conditions are encompassed in this limitation. What conditions qualify as 'stringent conditions' and whether or not low, medium and/or high stringency conditions are encompassed in the limitation, is not clear.

(c) Claims 2 and 5 lack proper antecedent basis in the limitation: 'An isolated polynucleotide according to Claim 1'. For proper antecedence, it is suggested that Applicant replace the phrase with --The isolated polynucleotide of claim 1--.

(d) Claims 8, 14 and 23 lack proper antecedent basis in the limitation: 'a polynucleotide of Claim 1'. For proper antecedence, it is suggested that Applicant replace the phrase with --the polynucleotide of claim 1--.

(e) In claims 3 and 5, for the purpose of distinctly claiming the subject matter, it is suggested that Applicant replace the limitation 'given herein as' with the limitation --of--.

(f) Claims 9 and 10 lack proper antecedent basis in the limitation 'an expression vector according to Claim 8'. For proper antecedence, it is suggested that Applicant replace the phrase with --the expression vector of claim 8--.

(g) Claim 25 lacks proper antecedent basis in the limitation 'an expression vector of Claim 8'. For proper antecedence, it is suggested that Applicant replace the phrase with --the expression vector of claim 8--.

(h) Claim 10 is vague and/or confusing in the limitation: 'DsrA'. Claim 10 depends from claim 8, which in turn depends from claim 1, which already recites a 'DsrA'. Does it mean that the 'DsrA' recited in claim 10 is of different scope than the one recited in the independent claim 1, from which it depends?

(i) Claims 15 and 16 lack proper antecedent basis in the limitation 'an antisense oligonucleotide of Claim 14'. For proper antecedence, it is suggested that Applicant replace the phrase with --the antisense oligonucleotide of claim 14--.

(j) Claim 17 is vague and indefinite in the recitation 'fragment', because it is unclear what is encompassed in this limitation. What constitutes a 'fragment' and how much of the protein's or the polynucleotide's original structure has to be retained such that the resulting

product qualifies as a 'fragment' is not clear. The metes and bounds of the structure encompassed in the limitation 'fragment' are indeterminate.

(k) Claim 15 is vague, indefinite and/or confusing in the limitation: 'DNA encoding an antisense oligonucleotide', because it is unclear how a DNA can encode an oligonucleotide, as opposed to a polypeptide or an oligopeptide.

(l) Claim 18 is vague, indefinite and/or confusing in the limitation: 'the polynucleotide sequence which encodes a polynucleotide', because it is unclear how a polynucleotide can encode a polynucleotide, as opposed to a polypeptide.

(m) Claim 18 is vague and indefinite in the recitation 'complement', because it is unclear what is encompassed in this limitation. In the absence of a size limit, what constitutes a 'complement' and how much of the polynucleotide's original structure has to be retained such that the resulting product qualifies as a 'complement' is not clear.

(n) Claim 18 is further vague, indefinite and inconsistent in the recitations: 'method for detecting a polynucleotide .... in a biological sample' and 'hybridizing to nucleic acid material of a biological sample'. What is encompassed in the 'nucleic acid material' and how it differs in scope from the 'polynucleotide' present in a biological sample is not clear.

(o) Claim 18 is vague, indefinite and/or lacks proper antecedent basis in the limitation: 'a polynucleotide encoding DsrA' (see the end of part b). Whether or not this 'a polynucleotide encoding DsrA' is the same as or different from the one recited in line 1 of the claim is not clear.

(p) Claim 24 lacks proper antecedent basis in the limitation 'A vaccine composition according to Claim 24'. For proper antecedence, it is suggested that Applicant replace the phrase with --The vaccine composition of claim 23--.

(q) Claim 24 is vague and indefinite in the limitation: 'polynucleotide has the sequence of SEQ ID NO: 1' without particularly reciting that SEQ ID NO: 1 is the --nucleotide sequence-- as opposed to the 'sequence'.

(r) Claim 28 is vague, indefinite and inconsistent in the limitation: 'inducing protective immune response' in lines 1 and 2 of the claim and the limitation: 'induce an immune response' in the last line of the claim. It is unclear how an amount of vaccine sufficient to induce a mere

'immune response' can result in a 'method of inducing a protective immune response' upon administration to a subject as recited.

(s) Claim 28 lacks proper antecedent basis in the limitation: 'a vaccine according to Claim 24'. For proper antecedence, it is suggested that Applicant replace the phrase with --the vaccine of claim 24--.

(t) Claims 2, 3, 5, 8-10, 14-18, 23-25 and 28, which depend directly or indirectly from claim 1, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

13) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14) Claims 1, 2, 8-10 and 14-16 are rejected under 35 U.S.C § 102(b) as being anticipated by Skurnik *et al.* (*Mol. Microbiol.* 3: 517-529, 1989 – Applicants' IDS).

It is noted that the limitation 'DsrA' in part (c) or (d) of claim 1 has no structure or size limit. As described in the second full paragraph on page 30 of the instant specification, the limitation 'DsrA' is not limited to the 'entire DsrA protein', but encompasses DsrA fragments and/or antigenic determinants. It is further noted that the scope of the recitation 'stringent conditions' is not limited to only high stringency conditions, but also encompasses unspecified low and medium stringency conditions.

Skurnik *et al.* taught an isolated gene or polynucleotide comprising several stretches 12-15 contiguous nucleotide sequences, GGTGTAGGCAAA, GTAGGAGGTTATAGA, GCATTAGCCATTGGT, and AAAGCGGGTGTAGCG encoding the DsrA, GlyValGlyLys, ValGlyGlyTyrArg, AlaLeuAlaIleGly, and LysAlaGlyValAlaTyr, as well as a single-stranded probe thereof, recombinant plasmids comprising the same, and an *E. coli* cell transformed with the plasmid. See 'Experimental procedures'; Figures 2-6; page 526, left column, first full

paragraph; and 'Results'. These stretches of contiguous nucleotides from the prior art polynucleotide are 100% identical in structure to several stretches of contiguous nucleotides from the instantly recited nucleotide sequence of SEQ ID NO: 1. See the attached sequence alignment report. The above-identified amino acid DsrA sequences structurally match DsrA fragments and/or antigenic determinants from the instantly recited SEQ ID NO: 2. Therefore, the prior art polynucleotide is expected to hybridize with the instantly recited SEQ ID NO: 1 at least under low stringency conditions and is expected comprise an antisense oligonucleotide therein of sufficient length that is complementary thereto.

Claims 1, 2, 8-10 and 14-16 are anticipated by Skurnik *et al.*

Objection(s)

15) The limitation 'Claim1' in claims 2 and 5 is objected to for not leaving a space before '1'. To be correct and to be consistent with the claim language used in claims 8 and 23, it is suggested that Applicants replace the limitation with --claim 1--.

Remarks

16) Claims 1-3, 5, 8-10, 14-18, 23-25 and 28 stand rejected.

An isolated polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1 is free of prior art currently of record.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and papers is (571) 273-8300.

18) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the

Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

July, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER

SEQ ID NO. 1

A;Residues: 1-434 <ROS>
A;Cross-references: EMBL:X12758; EMBL:X13883; NID:g48639; PIDN:CAA32088.1; PID:g48640
R;Skurnik, M.; Wolf-Watz, H.
Mol. Microbiol. 3, 517-529, 1989
A;Title: Analysis of the yopA gene encoding the Yop1 virulence determinants of Yersin
A;Reference number: S04910; MUID:89343638; PMID:2761389
A;Accession: S04910
A;Status: preliminary
A;Molecule type: DNA
A;Residues: 1-434 <SKU>
A;Cross-references: EMBL:X12758; EMBL:X13883; NID:g48639; PIDN:CAA32088.1; PID:g48640
C;Genetics:
A;Gene: yopA
A;Genome: plasmid

Alignment Scores:

Pred. No.:	1.41e-07	Length:	434
Score:	182.00	Matches:	41
Percent Similarity:	57.14%	Conservative:	19
Best Local Similarity:	39.05%	Mismatches:	41
Query Match:	8.89%	Indels:	4
DB:	2	Gaps:	2

US-10-030-529A-1 (1-1168) x S04534 (1-434)

```
Qy        557 AAATATTTACTAGAACTGGGTACTTATTTAGATGATTCTTATCGTATGATGGAACAAAAT 616
              |||   :::  |||        |||  |||     :::     ::::::
Db        334 LysAlaIleSerGluSerAsnGlnTyrThrAspHisLysPheSerGlnLeuAsp------ 351

Qy        617 ACACATAATATCAATAAGTTGTCTAAAGAATTGCAAACTGGTTTAGCCAACCAATCAGCA 676
                :::   :::::||||||   |||  :::      |||||||||:::   :::|||
Db        352 ---AsnArgLeuAspLysLeuAspLysArgValAspLysGlyLeuAlaSerSerAlaAla 370

Qy        677 TTGTCTATGTTAGTGCAACCAAATGGTGTAGGCAAAACGAGCGTTTCTGCTGCGGTAGGA 736
              |||:::   |||   ||||||   |||||||||||   :::   :::|||   ||||||
Db        371 LeuAsnSerLeuPheGlnProTyrGlyValGlyLysValAsnPheThrAlaGlyValGly 390

Qy        737 GGTTATAGAGATAAAACTGCATTAGCCATTGGTGTCGGCTCACGCATTACTGATCGCTTT 796
              |||||||||          ||||||||||||||   |||   |||:::   :::
Db        391 GlyTyrArgSerSerGlnAlaLeuAlaIleGlySerGlyTyrArgValAsnGluSerVal 410

Qy        797 ACCGCTAAAGCGGGTGTAGCGTTCAATACCTACAATGGCGGCATGTCTTATGGTGCTTCT 856
                  ||||||||||||||:::        :::      :::   |||   ||||||
Db        411 AlaLeuLysAlaGlyValAlaTyr---AlaGlySerSerAsnValMetTyrAsnAlaSer 429

Qy        857 GTTGGTTATGAATTC 871
                     |||:::
Db        430 PheAsnIleGluTrp 434
```